

## **NIGMS Scientific Advance**

**Project Title:** Proinflammatory Adaptive Cytokine and Shed Tumor Necrosis Factor Receptor Levels Are Elevated Preceding Systemic Lupus Erythematosus Disease Flare

**Institution and State:** Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma

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**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects millions of people worldwide, particularly women and minorities. Most SLE patients experience periods of intensified clinical disease activity, called flares, as the result of increased inflammation causing more severe clinical symptoms and irreversible organ damage. Inflammation can be caused by multiple soluble mediators, including cytokines, chemokines, and shed tumor necrosis receptor (TNFR) superfamily members. Understanding how these molecules change prior to intensified clinical disease activity will improve our ability to identify SLE patients at risk of flare and develop preventative treatments.

**Advance:** This study addressed how plasma levels of 52 cytokines, chemokines, and cleaved soluble TNFR superfamily members are altered prior to and concurrent with clinical SLE flare, as defined by the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). The participants in this study were female, European-American SLE patients from the SLE Influenza Vaccination study cohort. Soluble mediators were compared in patients who experienced a disease flare 6-12 weeks after providing a plasma sample (pre-flare samples), in gender, race, and age ( $\pm$  5 years) matched SLE patients who did not experience a disease flare within 6-12 weeks (non-flare samples), and in gender, race, and age ( $\pm$  5 years) matched unrelated, healthy individuals (control samples). In addition, plasma soluble mediator levels were compared in a subset of 13 SLE patients during comparable pre-flare and (self) non-flare periods in the same patient.

This analysis revealed immunomodulatory pathways that differ between pre-flare and non-flare periods. Significantly elevated levels of 23 soluble mediators were observed in plasma samples from pre-flare SLE patients compared to matched, unique non-flare or self-non-flare SLE patients and matched healthy individuals. Altered pre-flare mediators were also seen at time of disease flare, usually with no significant change in analyte levels compared to the pre-flare period, including multiple innate and adaptive cytokines from the Th1, Th2, and Th17 pathways, effector chemokines and soluble adhesion molecules, and soluble TNFR superfamily members. Non-flare samples had significantly elevated levels of regulatory mediators that have been shown to inhibit inflammation: interleukin-10 (IL-10), stromal cell-derived factor 1 (SDF-1), transforming growth factor beta (TGF- $\beta$ ), and IL-1 receptor agonist (IL-1Ra). Based on these differences, a soluble mediator score was developed as a simple way to compare the overall balance of pro-inflammatory and regulatory mediators. The soluble mediator score was significantly higher in pre-flare samples compared to non-flare samples, even within the same patient, suggesting that the soluble mediator score could become a useful clinical tool for identifying SLE patients at risk of an imminent flare.

**How the IDeA Program Grant Enabled Advance:** The U54GM104938 provided funding which supported in part the clinical research infrastructure to recruit and clinically characterize the patients and controls used in the study. In addition, the P30GM103510 supports the OMRF Serum Analyte

and Biomarker Core, led by Dr. Munroe, which performed the cytokine, chemokine, soluble TNF receptors and other plasma biomarkers assessed in the study. Personnel from this P30GM103510 supported core assay development, quality control and initial data processing. Personnel from this P30GM103510 Administrative Core also supported the data analysis in the study. The assistance of U54GM104938 and P30GM103510 remain invaluable resources in advancing knowledge in the field of SLE pathogenesis.

**Public Health Impact Statement:** This study gave new insight into immunomodulatory pathways that are influence intensified disease activity and clinical disease flare in SLE patients. The development of the soluble mediator score has linked the contribution of immune mediators with the risk of disease flare. With this greater understanding, we can better predict the occurrence of SLE disease flare and provide more effective clinical care for SLE patients.

**NIH Director's Theme(s) Relevance:** This project is directly relevant to the Director's theme of: (2) Emphasizing the translation of research into medicine. Building on basic science discoveries and utilizing samples from well-phenotyped patients, this study will assist providers in identifying patients at the highest risk of an upcoming disease flare allowing for pro-active management of disease on an individual basis.

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**Key words:** autoimmunity, systemic lupus erythematosus, disease flare, autoimmune disease, biomarkers.

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